

Final report-Teratologic Evaluation of FDA 71-13 (Ghatti Gum) in Mice, Rats,
Hamsters & Rabbits

8/1/72

M I C E

Food and Drug Research Laboratories
INCORPORATED



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**FINAL
REPORT**

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date August 1, 1972

Laboratory No. 0893 c
Contract No. FDA 71-260

Sample: Fine tan powdered material

Marking: FDA 71-13 (Gum ghatti)

Examination Requested: Teratologic evaluation of FDA 71- 13 in mice.

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings,
the following is concluded:

"The administration of up to 1700 mg/kg (body weight) of the test material to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

Comment: Attention is called to the fact that this is the seventh of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs: each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morganeidge
Kenneth Morganeidge, Ph.D.
Vice President

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 61 & 62; 67 through 70

Material: FDA 71-13

Table 1

Fate Summary
(Mice)

Date June 15, 1972

Laboratory No. 0893 c

Group	Material	Dose ** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
61	Sham	0	25	20	23	18
62	Aspirin*	150	22	20	21	19
67	FDA 71-13	17	26	21	26	21
68	FDA 71-13	80	23	21	21	19
69	FDA 71-13	370	25	20	25	20
70	FDA 71-13	1700	29	21	28	20

* Positive Control

** Administered as a suspension in anhydrous corn oil; 1.0 ml per kg of body weight

FOOD & DRUG RESEARCH LABORATORY, INC.

Group: 61 & 62; 67 through 70

Date June 15, 1972

Material: FDA 71-13

Table 2
Reproduction Data
(Mice)

Laboratory No. 0893 c

Group:	61	62	67	68	69	70
Dose (mg/kg):	Sham	Aspirin**	17	80	370	1700

Pregnancies

Total No.	20	20	21	21	20	21
Died or aborted (before Day 17)	2	1	0	2	0	1
To term (on Day 17)	18	19	21	19	20	20

Corpora lutea

Total No.						
Average/dam mated						

Live litters

Total No.*	18	19	21	19	19	20
------------	----	----	----	----	----	----

Implant sites

Total No. (at term)	198	201	254	215	224	237
Average/dam*	11.0	10.6	12.1	11.3	11.2	11.9

Resorptions

Total No.*	7	8	19	11	16	12
Dams with 1 or more sites resorbed	7	6	11	7	7	9
Dams with all sites resorbed	0	0	0	0	1	0
Per cent partial resorptions	38.9	31.6	52.4	36.8	35.0	45.0
Per cent complete resorptions	--	--	--	--	5.00	--

Live fetuses

Total No. (at term)	188	187	233	203	207	222
Average/dam*	10.4	9.8	11.1	10.7	10.4	11.1

Dead fetuses

Total No.*	3	6	2	1	1	3
Dams with 1 or more dead	3	4	2	1	1	3
Dams with all dead	0	0	0	0	0	0
Per cent partial dead	16.7	21.1	9.52	5.26	5.00	15.0
per cent all dead	--	--	--	--	--	--

Average fetus weight, g	0.90	0.91	0.93	0.93	0.95	0.91
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* Includes only those dams examined at term.

** Positive control: 150 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 & 62; 67 through 70

Laboratory No. 0893 c

Table 3

Material FDA 71-13

Date June 15, 1972

Summary of Skeletal Findings
(Mice)

Findings	Group No. Dose (mg/kg)	61 Sham	62 Aspirin**	67 17	68 80	69 370	70 1700
Live Fetuses Examined (at term)		131/18	131/19	162/21	140/19	144/19	154/20
Sternebrae							
Incomplete oss.		38/14	57/16	56/18	41/12	19/7	38/15
Scrambled							
Bipartite		4/4	2/2	1/1	5/5	1/1	4/3
Fused							
Extra							
Missing		16/7	21/9	19/5			7/5
Other							
Ribs							
Incomplete oss.							
Fused/split							
Wavy							
Less than 12							
More than 13		29/12	7/4	8/8	14/7	13/7	11/6
Other							
Vertebrae							
Incomplete oss.							
Scrambled							
Fused							
Extra ctrs. oss.							1/1
Scoliosis							
Tail defects							
Other							
Skull							
Incomplete closure							3/1
Missing							
Cranioostosis							
Other; occipitals; incomplete							1/1
Extremities							
Incomplete oss.							
Missing							
Extra							
Miscellaneous							
Hyoid; missing		27/10	34/14	28/10	33/12	31/10	20/15
Hyoid; reduced		11/8	12/5	14/9	15/10	20/10	15/9

* Numerator=Number of fetuses affected; Denominator=Number of litters affected

** Positive control at 150 mg/kg

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Groups 61 & 62; 67 through 70

Date June 15, 1972

Material FDA 71-13

Laboratory No. 0893 c

Table 3-a
Summary of Soft Tissue Abnormalities
(Mice)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
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None Observed

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Groups 61 & 62; 67 through 70

Date June 15, 1972

Species Mice

Table 4

Laboratory No. 0893 c

Average Body Weights*

Group	Material	Dose Level mg/kg	Day-----				
			0	6	11	15	17**
			-----g-----				
61	Sham	0	27.4	29.9	31.6	39.3	45.8 (18)
62	Aspirin***	150	23.3	29.9	33.5	38.6	45.2 (19)
67	FDA 71-13	17	27.9	31.0	34.2	42.0	48.3 (21)
68	FDA 71-13	80	27.9	30.5	33.8	41.4	47.2 (19)
69	FDA 71-13	370	28.9	30.7	34.2	41.9	48.3 (20)
70	FDA 71-13	1700	28.2	32.9	33.3	41.3	46.2 (20)

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** Positive control:



Appendix I

Teratology Study in Mice

Virgin adult female albino CD-1 outbred mice were individually housed in disposable plastic cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 11, 15, and 17 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 17 all dams were subjected to Caesarean section under surgical anesthesia, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations employing 10X magnification. The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

Group 61

Appendix II

Date June 15, 1972Material Sham

Reproduction Data in Mice (Individual)

Laboratory No. 0893Dose 0

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
S 3181	NP		0						--	
S 3182	NP		0						--	
S 3183	P		13	12		--	--	1	0.70	
S 3184	P		11	10		--	--	1	0.76	
S 3185	NP		0						--	
S 3186	P		12	11	1	--	--		0.91	
S 3187	P		11	10		--	--	1	0.80	
S 3188	P		10	9		--	--	1	0.84	
S 3189	P		10	10		--	--		0.80	
S 3190	P		12	10	1	--	--	1	0.93	
S 3191	P		10	10		--	--		0.74	
S 3192	NP		0						--	
S 3193	P		12	12		--	--		0.84	
S 3194	P		12	12		--	--		0.82	
S 3195	NP		0						--	
S 3196	P		10	10		--	--		1.31	
S 3197	P		9	9		--	--		--	Aborted Day 14
S 3198	P		11	11		--	--		1.00	
S 3199	P		10	10		2	8		1.05	
S 3200	P		10	9		3	6	1	0.88	
S 3201	P		11	10	1	4	7		0.91	
S 3202	P		9	9		3	6		0.93	
S 3203	P		12	12		6	6		1.04	
S 3204	P		12	11		8	3	1	1.03	
S 3205	P		10	0	10	--	--		--	Died Day 13

* P = Pregnant; NP = Not Pregnant

FOOD & DRUG RESEARCH LABORATORIES, INC.

Group 62

Appendix II

Date June 15, 1972

Material Aspirin

Reproduction Data in Mice (Individual)

Laboratory No. 0893

Dose 150 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
A 3181	NP		0						--	
A 3182	P		11	9		--	--	2	1.29	
A 3183	P		13	12		--	--	1	0.76	
A 3184	P		12	10	1	--	--	1	0.88	
A 3185	P		15	0		--	--	15	--	Died Day 15
A 3186	P		11	11		--	--		0.72	
A 3187	NP		0						--	
A 3188	P		12	10		--	--	2	0.75	
A 3189	P		12	11		--	--	1	0.89	
A 3190	P		3	3		--	--		0.77	
A 3191	P		7	7		--	--		1.31	
A 3192	P		13	13		--	--		0.84	
A 3193	P		13	11	2	--	--		0.75	
A 3194	P		13	13		--	--		0.68	
A 3195	P		11	10	1	--	--		0.84	
A 3196	P		7	7		4	3		0.99	
A 3197	P		9	9		4	5		0.95	
A 3198	P		8	8		2	6		1.01	
A 3199	P		10	10		6	4		0.87	
A 3200	P		9	7	2	2	5		0.84	
A 3201	P		16	15		6	10	1	0.96	
A 3202	P		11	11		6	5		1.11	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORY, INC.

Group 67

Appendix II

Date June 15, 1972

Material FDA 71-13

Reproduction Data in Mice (Individual)

Laboratory No. 0893c

Dose 17 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
C 3001	P		17	16		--	--	1	0.72	
C 3002	P		13	12		--	--	1	0.88	
C 3003	P		13	12		--	--	1	0.84	
C 3004	P		11	7		--	--	4	0.92	
C 3005	NP		0						--	
C 3006	P		8	7	1	--	--		0.83	
C 3007	P		14	14		--	--		0.90	
C 3008	P		13	13		--	--		0.96	
C 3009	P		12	12		--	--		0.70	
C 3010	NP		0						--	
C 3011	NP		0						--	
C 3012	NP		0						--	
C 3013	P		14	10		5	5	4	1.05	
C 3014	P		11	10		2	8	1	1.01	
C 3015	P		12	10	1	4	6	1	1.07	
C 3016	P		13	12		5	7	1	0.93	
C 3017	P		11	11		5	6		0.98	
C 3018	P		9	9		4	5		1.02	
C 3019	P		9	9		3	6		1.00	
C 3020	P		14	14		5	9		1.02	
C 3021	P		11	9		4	5	2	0.95	
C 3022	P		12	11		5	6	1	0.95	
C 3023	P		11	9		4	5	2	0.90	
C 3024	NP		0						--	
C 3025	P		13	13		7	6		0.99	
C 3026	P		13	13		3	10		0.83	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 68

Appendix II

Date June 15, 1972

Material FDA 71-13

Reproduction Data in Mice (Individual)

Laboratory No. 0893c

Dose 80 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
C 3031	NP		0						--	
C 3032	P		12	12		--	--		0.74	
C 3033	P		13	12	1	--	--		0.79	
C 3034	P		11	7		--	--	4	0.76	
C 3035	P		13	13		--	--		0.68	
C 3036	P		12	11		--	--	1	0.85	
C 3037	P		12	12		--	--		0.81	
C 3038	P		11	11		--	--		1.01	
C 3039	P		8	7		--	--	1	1.12	
C 3040	P		9	9		--	--		1.07	
C 3041	P		10	10		--	--		--	Aborted Day 15
C 3042	NP		0						--	
C 3043	P		11	11		--	--		0.83	
C 3044	P		9	8		--	--	1	--	Aborted Day 14
C 3045	P		12	12		5	7		1.02	
C 3046	P		12	11		3	8	1	0.99	
C 3047	P		11	11		8	3		0.99	
C 3048	P		8	8		3	5		0.95	
C 3049	P		11	10		4	6	1	1.02	
C 3050	P		13	13		7	6		0.82	
C 3051	P		13	12		7	5	1	1.08	
C 3052	P		13	13		6	7		1.09	
C 3053	P		10	8		3	5	2	1.11	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 69

Appendix II

Date June 15, 1972

Material FDA 71-13

Reproduction Data in Mice

(Individual)

Laboratory No. 0893c

Dose 370 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
C 3061	P		12	11		--	--	1	0.72	
C 3062	NP		0						--	
C 3063	NP		0						--	
C 3064	P		13	10		--	--	3	0.83	
C 3065	P		7	0		--	--	7	--	
C 3066	P		14	14		--	--		0.80	
C 3067	P		10	10		--	--		0.85	
C 3068	P		11	10	1	--	--		0.94	
C 3069	P		10	10		--	--		0.85	
C 3070	P		13	13		--	--		0.91	
C 3071	P		11	10		--	--	1	1.01	
C 3072	P		9	9		--	--		1.02	
C 3073	P		12	12		--	--		1.06	
C 3074	NP		0						--	
C 3075	NP		0						--	
C 3076	P		11	11		4	7		0.94	
C 3077	P		14	12		5	7	2	0.97	
C 3078	P		12	12		8	4		0.92	
C 3079	P		7	6		5	1	1	1.02	
C 3080	P		11	11		4	7		1.09	
C 3081	P		12	12		4	8		0.97	
C 3082	P		12	12		3	9		1.10	
C 3083	NP		0						--	
C 3084	P		12	12		7	5		1.11	
C 3085	P		11	10		4	6	1	1.00	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 70

Appendix II

Date June 15, 1972

Material FDA 71-13

Reproduction Data in Mice (Individual)

Laboratory No. 0893c

Dose 1700 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
C 3091	NP		0						--	
C 3092	NP		0						--	
C 3093	NP		0						--	
C 3094	P		11	11		--	--		0.81	
C 3095	P		13	9	1	--	--	3	0.94	
C 3096	P		13	13		--	--		0.94	
C 3097	P		11	10		--	--	1	0.72	
C 3098	P		8	8		--	--		0.79	
C 3099	P		11	11		--	--		0.91	
C 3100	P		10	9		--	--	1	0.76	
C 3101	P		10	10		--	--		0.98	
C 3102	P		10	10		--	--		1.13	
C 3103	NP		0						--	
C 3104	NP		0						--	
C 3105	NP		0						--	
C 3106	P		10	9	1	3	6		0.86	
C 3107	NP		0						--	
C 3108	P		13	12		5	7	1	0.97	
C 3109	P		9	8		2	6	1	1.01	
C 3110	P		11	11		--	--		--	Died Day 15
C 3111	P		14	12		6	6	2	0.89	
C 3112	P		19	18		12	6	1	0.93	
C 3113	P		9	8		4	4	1	0.97	
C 3114	P		14	14		7	7		0.99	
C 3115	P		15	15		7	8		0.81	
C 3116	P		12	12		5	7		0.91	
C 3117	NP		0						--	
C 3118	P		13	13		4	9		0.91	
C 3119	P		12	10	1	3	8	1	0.88	

* P = Pregnant; NP = Not Pregnant

R A T S

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INCORPORATED



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FINAL REPORT

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date August 1, 1972

Laboratory No. 0894 c
Contract No. FDA 71-260

Sample: Fine tan powdered material

Marking: FDA 71-13 (Gum ghatti)

Examination Requested: Teratologic evaluation of FDA 71-13 in rats

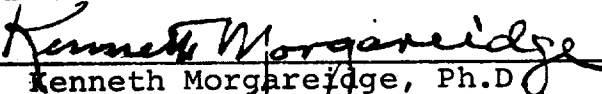
Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 370 mg/kg (body weight) of the test material as a suspension in anhydrous corn oil to pregnant rats for 10 consecutive days had no discernible effect on nidation or on maternal or fetal survival. The number and type of abnormalities seen in fetal soft or skeletal tissues derived from this group of dams did not differ from the number occurring spontaneously in the sham-treated controls. However, in a group of dams dosed at 1700 mg/kg (body weight), significant maternal toxicity ensued with the loss of 5 out of 24 pregnant rats. Death was accompanied by severe diarrhea and urinary incontinence with anorexia for 48 to 72 hours terminally. At autopsy, no gross pathological findings were seen other than marked petechial hemorrhage in the mucosa of the small intestine. Rats which survived this high dose and bore living young to term remained outwardly normal and the offspring were likewise normal in all respects. It is concluded that this test substance was not a teratogen in the rat.

FOOD AND DRUG RESEARCH LABORATORIES, INC.


Kenneth Morgareidge, Ph.D.
Vice President

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Comment: Attention is called to the fact that this is the seventh of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 61 & 62; 67 through 70

Date June 15, 1972

Material: FDA 71-13

Table 1
Fate Summary
(Rats)

Laboratory No. 0894 c

Group	Material	Dose** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
61	Sham	0	27	24	23	21
62	Aspirin*	250	24	20	22	18
67	FDA 71-13	17	25	21	25	21
68	FDA 71-13	80	22	21	21	20
69	FDA 71-13	370	24	22	23	21
70	FDA 71-13	1700	24	21	19	17

* Positive Control

** Administered as a suspension in anhydrous corn oil; 1.0 ml per kg of body weight

Group: 61 & 62; 67 through 70

FOOD & DRUG RESEARCH LABORATORIES, INC.

Date June 15, 1972Material: FDA 71-13Table 2
Reproduction Data
(Rats)Laboratory No. 0894 c

Group:	61	62	67	68	69	70
Dose (mg/kg):	Sham	Aspirin**	17	80	370	1700
Pregnancies						
Total No.	24	20	21	21	22	21
Died or aborted (before Day 20)	4	2	0	1	1	5
To term (on Day 20)	21	18	21	20	21	17
Corpora lutea						
Total No.						
Average/dam mated						
Live litters						
Total No.*	21	17	21	20	21	17
Implant sites						
Total No. (at term)	218	194	264	225	220	191
Average/dam*	10.4	10.8	12.6	11.3	10.5	11.2
Resorptions						
Total No.*	5	18	2	5	5	2
Dams with 1 or more sites resorbed	4	7	1	2	2	1
Dams with all sites resorbed	0	1	0	0	0	0
Per cent partial resorptions	19.0	38.9	4.76	10.0	9.52	5.88
Per cent complete resorptions	----	5.55	----	----	----	----
Live fetuses						
Total No. (at term)	213	174	262	219	215	189
Average/dam*	10.1	9.67	12.5	11.0	10.2	11.1
Dead fetuses						
Total No.*	0	2	0	1	0	0
Dams with 1 or more dead	----	1	----	1	----	----
Dams with all dead	----	0	----	0	----	----
Per cent partial dead	----	5.55	----	5.00	----	----
per cent all dead	----	----	----	----	----	----
Average fetus weight, g	3.97	2.52	4.13	3.95	4.01	4.02

* Includes only those dams examined at term.

** Positive control: 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 & 62; 67 through 70Laboratory No. 0894 c

Table 3

Material FDA 71-13Date June 15, 1972Summary of Skeletal Findings
(Rats)

Findings	Group No. Dose (mg/kg)	61 Sham	62 Aspirin**	67 17	68 80	69 370	70 1700
Live Fetuses Examined (at term)		148/21	112/17	179/21	154/20	152/21	131/17
Sternebrae							
Incomplete oss.		25/14	60/15	29/11	24/11	40/14	40/15
Scrambled		3/3					
Bipartite			18/9				
Fused							
Extra			1/1				
Missing		2/2	74/15	5/5	3/3	4/4	10/6
Other							
Ribs							
Incomplete oss.				1/1			3/3
Fused/split		1/1	5/3				
Wavy		6/4	33/11	7/5	9/7	24/14	9/3
Less than 12							
More than 13		30/14	38/12	2/2	6/5	12/7	
Other							
Vertebrae							
Incomplete oss.		9/4	71/16	12/5		2/1	19/8
Scrambled			6/5				
Fused			2/1				
Extra ctrs. oss.							
Scoliosis			11/7				1/1
Tail defects							
Other							
Skull							
Incomplete closure		3/2	13/7	13/8	8/5		3/3
Missing							
Cranioostosis							
Other; exencephally			2/1				
Extremities							
Incomplete oss.			4/3				
Missing							
Extra							
Miscellaneous							
Hyoid; missing		11/8	49/14	13/9	7/4	16/8	4/2
Hyoid; reduced		5/5	10/6	12/6	17/11	15/9	11/5

* Numerator=Number of fetuses affected; Denominator=Number of litters affected

** Positive control at 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 & 62; 67 through 70

Date June 15, 1972

Material FDA 71-13

Laboratory No. 0894 c

Table 3-a
Summary of Soft Tissue Abnormalities
(Rats)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
62	Aspirin*	250	A 4183	1	Meningoencephalocele
			A 4185	1	Meningoencephalocele
			A 4188	2	Meningoencephalocele, Anopia, Spina Bifida
			A 4197	2	Meningoencephalocele, Anopia, Spina Bifida
			A 4201	2	Meningoencephalocele, Anopia, Spina Bifida
			A 4204	4	Meningoencephalocele
68	FDA 71-13	80	C 4032	1	Medial rotation hind limbs

*Positive Control

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 & 62; 67 through 70

Date June 15, 1972

Species Rats

Table 4

Laboratory No. 0894 c

Average Body Weights *

Group	Material	Dose Level	Day				
			0	6	11	15	20**
		mg/kg	g				
61	Sham	0	213	231	249	272	332 (21)
62	Aspirin***	150	210	229	245	255	305 (18)
67	FDA 71-13	17	227	248	263	291	357 (21)
68	FDA 71-13	80	209	231	247	268	333 (20)
69	FDA 71-13	370	217	238	253	271	333 (21)
70	FDA 71-13	1700	213	235	252	270	335 (17)

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** Positive control:



Appendix I

Teratology Study in Rats

Virgin adult female albino rats (Wistar derived stock) were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 11, 15, and 20 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 20 all dams were subjected to Caesarean section under surgical anesthesia, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations employing 10X magnification. The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD & DRUG RESEARCH LABORATORIES, INC.

Appendix II

Date June 15, 1972Group 61Material Sham

Reproduction Data in Rats (Individual)

Laboratory No. 0894Dose 0

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
S 4181	P		11	11		--	--		3.81	
S 4182	P		12	12		--	--		3.98	
S 4183	P		10	10		--	--		3.69	
S 4184	P		10	10		--	--		3.72	
S 4185	P		13	13		--	--		4.31	
S 4186	P		9	9		--	--		3.84	
S 4187	P		10	10		7	3		5.34	
S 4188	P		10	9		6	3	1	4.08	
S 4189	P		11	11		7	4		3.84	
S 4190	P		13	13		7	6		3.93	
S 4191	P		10	10		--	--		----	Died Day 15
S 4192	P		9	7		3	4	2	3.44	
S 4193	P		10	10		--	--		----	Died Day 14
S 4194	P		15	0		--	--	15	----	Died Day 17
S 4195	P		9	9		5	4		3.84	
S 4196	NP		0						----	Died Day 13
S 4197	P		12	12		4	8		3.87	
S 4198	P		12	12		6	6		3.90	
S 4199	NP		0						----	
S 4200	NP		0						----	
S 4201	P		10	10		6	4		3.49	
S 4202	P		9	9		5	4		3.74	
S 4203	P		9	9		7	2		4.20	
S 4204	P		13	13		4	9		4.00	
S 4205	P		8	8		5	3		4.12	
S 4206	P		6	5		3	2	1	4.08	
S 4207	P		12	11		5	6	1	4.13	

* P = Pregnant; NP = Not Pregnant

FOOD & DRUG RESEARCH LABORATORIES, INC.

Group 62

Appendix II

Date June 15, 1972

Material Aspirin

Reproduction Data in Rats (Individual)

Laboratory No. 0894

Dose 250 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
A 4181	P		13	13		--	--		2.43	
A 4182	P		12	12		--	--		2.98	
A 4183	P		10	8		--	--	2	2.17	
A 4184	P		11	11		--	--		2.95	
A 4185	P		10	10		--	--		2.46	
A 4186	P		6	6		--	--		1.96	
A 4187	NP		0						----	
A 4188	P		12	10		5	5	2	1.97	
A 4189	P		14	14		--	--		----	Died Day 18
A 4190	P		13	13		9	4		2.12	
A 4191	P		9			--	--	9	----	
A 4192	P		15	15		8	7		3.21	
A 4193	P		12	12		7	5		3.07	
A 4194	P		10	10		4	6		3.39	
A 4195	P		15	15		--	--		----	Died Day 10
A 4196	P		9	8		5	3	1	2.82	
A 4197	P		10	9		4	5	1	1.98	
A 4198	NP		0						----	
A 4199	NP		0						----	
A 4200	NP		0						----	
A 4201	P		11	7	2	3	4	2	1.92	
A 4202	P		13	13		7	6		2.58	
A 4203	P		5	4		1	3	1	2.56	
A 4204	P		13	13		5	8		2.34	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 67

Appendix II

Date June 15, 1972Material FDA 71-13

Reproduction Data in Rats (Individual)

Laboratory No. 0894 cDose 17 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
C 4001	P		14	14		--	--		3.75	
C 4002	P		11	11		--	--		4.20	
C 4003	NP		0						----	
C 4004	P		12	12		5	7		3.95	
C 4005	P		13	13		5	8		3.92	
C 4006	P		13	13		6	7		3.61	
C 4007	NP		0						----	
C 4008	P		16	16		5	11		5.99	
C 4009	P		15	15		5	10		3.90	
C 4010	NP		0						----	
C 4011	P		12	12		4	8		3.95	
C 4012	P		9	9		3	6		5.70	
C 4013	P		9	9		6	3		4.32	
C 4014	P		16	16		7	9		3.83	
C 4015	P		14	14		6	8		3.48	
C 4016	P		12	12		6	6		4.21	
C 4017	P		9	9		3	6		3.70	
C 4018	P		12	12		4	8		3.67	
C 4019	P		10	10		7	3		3.70	
C 4020	P		11	11		8	3		4.25	
C 4021	NP		0						----	
C 4022	P		13	13		4	9		5.48	
C 4023	P		15	15		7	8		3.82	
C 4024	P		14	14		5	9		3.43	
C 4025	P		14	12		7	5	2	3.91	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 68

Appendix II

Date June 15, 1972

Material FDA 71-13

Reproduction Data in Rats (Individual)

Laboratory No. 0894 c

Dose 80 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
C 4031	P		11	11		--	--		3.90	
C 4032	P		1	1		--	--		4.03	
C 4033	P		11	11		7	4		4.06	
C 4034	P		15	15		9	6		3.97	
C 4035	P		13	13		7	6		4.16	
C 4036	P		7	7		1	6		3.99	
C 4037	P		10	10		7	3		4.45	
C 4038	NP		0						----	
C 4039	P		9	9		4	5		3.94	
C 4040	P		12	12		5	7		3.94	
C 4041	P		12	8		4	4	4	4.25	
C 4042	P		10	10		--	--		----	Died Day 12
C 4043	P		10	8	1	2	7	1	4.00	
C 4044	P		11	11		8	3		3.97	
C 4045	P		12	12		4	8		3.56	
C 4046	P		12	12		2	10		3.54	
C 4047	P		16	16		5	11		3.81	
C 4048	P		12	12		8	4		3.74	
C 4049	P		14	14		6	8		4.81	
C 4050	P		12	12		9	3		3.55	
C 4051	P		10	10		5	5		3.41	
C 4052	P		15	15		6	9		3.86	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 69

Appendix II

Date June 15, 1972Material FDA 71-13

Reproduction Data in Rats (Individual)

Laboratory No. 0894 cDose 370 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
C 4061	P		10	10		--	--		4.17	
C 4062	NP		0						----	
C 4063	NP		0						----	
C 4064	P		8	8		3	5		3.43	
C 4065	P		10	10		5	5		4.09	
C 4066	P		11	11		3	8		4.15	
C 4067	P		13	13		7	6		3.57	
C 4068	P		7	7		1	6		3.74	
C 4069	P		14	14		10	4		3.68	
C 4070	P		9	9		4	5		3.84	
C 4071	P		11	11		5	6		4.29	
C 4072	P		11	11		5	6		3.92	
C 4073	P		6	6		3	3		5.63	
C 4074	P		10		4	--	--	6	----	Died Day 13
C 4075	P		13	13		7	6		3.36	
C 4076	P		10	10		4	6		5.32	
C 4077	P		6	6		3	3		4.03	
C 4078	P		12	11		8	3	1	3.72	
C 4079	P		7	3		2	1	4	3.74	
C 4080	P		12	12		4	8		3.36	
C 4081	P		13	13		5	8		3.87	
C 4082	P		14	14		6	8		4.34	
C 4083	P		10	10		5	5		3.84	
C 4084	P		13	13		8	5		4.11	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 70

Appendix II

Date June 15, 1972

Material FDA 71-13

Reproduction Data in Rats (Individual)

Laboratory No. 0894 c

Dose 1700 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks**
				Alive	Dead	M	F			
C 4091	P		14	14		--	--		3.57	
C 4092	P		8	8		--	--		4.13	
C 4093	P		9	9		5	4		4.11	
C 4094	P		10	10		3	7		3.98	
C 4095	P		15	15		11	4		3.97	
C 4096	P		12			--	--	12	----	Died Day 19
C 4097	P		9	9		5	4		4.06	
C 4098	P		11	11		4	7		6.19	
C 4099	P		12	10		3	7	2	3.88	
C 4100	P		9	9		--	--		----	Died Day 13
C 4101	P		14	14		--	--		----	Died Day 11
C 4102	NP		0						----	Died Day 13
C 4103	P		12	12		--	--		----	Died Day 9
C 4104	P		12	12		7	5		3.86	
C 4105	NP		0						----	
C 4106	P		13	13		9	4		3.99	
C 4107	P		7	7		5	2		4.20	
C 4108	P		11	11		5	6		3.90	
C 4109	P		12	12		4	8		3.33	
C 4110	P		15	15		6	9		3.66	
C 4111	P		10	10		5	5		4.07	
C 4112	NP		0						----	
C 4113	P		13	13		6	7		3.72	
C 4114	P		10	10		5	5		3.77	

* P = Pregnant; NP = Not Pregnant

** Toxic death (see page 1)

HAMSTERS

Food and Drug Research Laboratories
I N C O R P O R A T E D



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**F I N A L
R E P O R T**

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date August 1, 1972

Laboratory No. 0895 c
Contract No. FDA 71-260

Sample: Fine tan powdered material

Marking: FDA 71-13 (Gum ghatti)

Examination Requested: Teratologic evaluation of FDA 71-13 in hamsters

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 1700 mg/kg (body weight) of the test material to pregnant hamsters for 5 consecutive days had no clearly discernable effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

Comment: Attention is called to the fact that this is the seventh of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.


Kenneth Morgareidge, Ph.D.

Vice President

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FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 61 & 62; 67 through 70

Material: FDA 71-13

Table 1

Fate Summary
(Hamsters)

Date June 15, 1972

Laboratory No. 0895 c

Group	Material	Dose** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
61	Sham	0	21	20	20	19
62	Aspirin*	250	21	20	20	19
67	FDA 71-13	17	20	20	20	20
68	FDA 71-13	80	23	20	23	20
69	FDA 71-13	370	22	20	22	20
70	FDA 71-13	1700	20	20	20	20

* Positive Control

** Administered as a suspension in anhydrous corn oil; 1.0 ml per kg of body weight

Group: 61 & 62; 67 through 70

FOOD & DRUG RESEARCH LABORATORY, INC.

Date June 15, 1972Material: FDA 71-13

Table 2
Reproduction Data
(Hamsters)

Laboratory No. 0895 c

Group:	61	62	67	68	69	70
Dose (mg/kg):	Sham	Aspirin**	17	80	370	1700
Pregnancies						
Total No.	20	20	20	20	20	20
Died or aborted (before Day 14)	1	1	0	0	0	0
To term (on Day 14)	19	19	20	20	20	20
Corpora lutea						
Total No.						
Average/dam mated						
Live litters						
Total No.*	19	19	20	20	20	19
Implant sites						
Total No. (at term)	242	238	248	247	256	256
Average/dam*	12.7	12.5	12.4	12.4	12.8	12.8
Resorptions						
Total No.*	5	11	12	10	13	15
Dams with 1 or more sites resorbed	3	9	6	7	10	4
Dams with all sites resorbed	0	0	0	0	0	1
Per cent partial resorptions	15.8	47.4	30.0	35.0	50.0	20.0
Per cent complete resorptions	----	----	----	----	----	5.00
Live fetuses						
Total No. (at term)	236	226	236	236	242	240
Average/dam*	12.4	11.9	11.8	11.8	12.1	12.0
Dead fetuses						
Total No.*	1	1	0	1	1	1
Dams with 1 or more dead	1	1	----	1	1	1
Dams with all dead	0	0	----	0	0	0
Per cent partial dead	5.26	5.26	----	5.00	5.00	5.00
per cent all dead	----	----	----	----	----	----
Average fetus weight, g	1.83	1.84	1.95	1.87	1.93	1.90

* Includes only those dams examined at term.

** Positive control: 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 & 62; 67 through 70

Laboratory No. 0895 c

Table 3

Material FDA 71-13

Date June 15, 1972

Summary of Skeletal Findings*
(Hamsters)

Findings	Group No. Dose (mg/kg)	61 Sham	62 Aspirin**	67 17	68 80	69 370	70 1700
Live Fetuses Examined (at term)		161/19	156/19	165/20	168/20	166/20	165/19
Sternebrae							
Incomplete oss.		71/17	65/15	44/17	54/16	72/19	39/15
Scrambled							
Bipartite		33/14	25/15	22/14	11/8	14/8	27/15
Fused							
Extra			7/2	5/4	11/5	10/7	9/7
Missing		59/14	26/12	8/7	9/7	4/3	13/5
Other							
Ribs							
Incomplete oss.							
Fused/split							
Wavy			1/1				
Less than 12							
More than 13		19/10	43/12	13/8	54/16	51/18	46/17
Other							
Vertebrae							
Incomplete oss.							
Scrambled				1/1			
Fused							
Extra ctrs. oss.							1/1
Scoliosis			6/3	2/2			1/1
Tail defects							
Other							
Skull							
Incomplete closure			2/2				
Missing							
Cranioostosis							
Other							
Extremities							
Incomplete oss.			1/1				
Missing							
Extra							
Miscellaneous							
Hyoid; missing		3/2	2/1	1/1			
Hyoid; reduced		3/3	4/3	1/1			1/1

* Numerator=Number of fetuses affected; Denominator=Number of litters affected
 ** Positive control at 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 & 62; 67 through 70

Date June 15, 1972

Material FDA 71-13

Laboratory No. 0835-c

Table 3-a
Summary of Soft Tissue Abnormalities
(Hamsters)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
62	Aspirin*	250	A 5188	1	Thoracic Subcutaneous Hematoma
69	FDA 71-13	370	C 5078	1	Medial rotation hind limbs
70	FDA 71-13	1700	C 5091	1	Sacral Subcutaneous Hematoma

*Positive Control

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 & 62; 67 through 70

Date June 15, 1972

Species Hamsters

Table 4

Laboratory No. 0895 c

Average Body Weights *

Group	Material	Dose Level mg/kg	-----Day-----				
			0	6	8	10	14**
			-----g-----				
61	Sham	0	104.6	109.1	111.2	123.2	148.2 (19) ^a
62	Aspirin***	250	109.3	110.5	110.0	121.2	145.8 (19) ^a
67	FDA 71-13	17	106.5	107.9	111.6	122.8	145.8 (20)
68	FDA 71-13	80	106.6	109.3	114.2	123.6	145.8 (20)
69	FDA 71-13	370	110.6	112.9	117.4	128.5	151.9 (20)
70	FDA 71-13	1700	105.8	109.0	111.6	121.2	144.1 (20)

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** Positive Control

^a Average based on weights of 18 dams only



Appendix I

Teratology Study in Hamsters

Virgin adult female golden hamsters from an outbred strain were individually housed in mesh bottom cages in temperature and humidity controlled quarters with free access to food and fresh tap water at all times. They were mated (1 to 1) with mature males and the appearance of motile sperm in the vaginal smear was considered as Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 10 of gestation, the indicated dose levels of the test material were administered by oral intubation; the controls were sham-treated.

Body weights were recorded on Days 0, 8, 10, and 14 of the gestation period. All animals were observed daily for appearance and behavior with particular attention to food consumption in order to better recognize any abnormalities resulting from anorexic effects in the pregnant animal.

On Day 14, all animals were subjected to Caesarian section under deep anesthesia and the numbers of implantation sites, resorption sites, live and dead fetuses were recorded. All live pups were weighed and the genital tract of each dam was examined for any anatomical abnormalities.

All fetuses were examined grossly for the presence of external congenital defects and one-third of each litter underwent detailed visceral examination under 10X magnification. The remaining two-thirds of the pups were cleared in potassium hydroxide, stained with alizarin red dye, and examined for the presence of skeletal abnormalities.

FOOD & DRUG RESEARCH LABORATORY, INC.

Group 61

Appendix II

Date June 15, 1972

Material Sham

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895

Dose 0

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M**	F**			
S 5181	P		12	12					2.25	
S 5182	P		19	17				2	1.76	
S 5183	P		9	9					1.85	
S 5184	P		11	11					2.09	Aborted Day 13
S 5185	P		13	13					1.84	
S 5186	P		13	11				2	1.90	
S 5187	P		14	14					1.73	
S 5188	P		14	13				1	2.08	
S 5189	P		13	13					1.86	
S 5190	P		11	11					1.95	
S 5191	P		10	10					1.91	
S 5192	P		13	13					2.12	
S 5193	P		13	12	1				1.51	
S 5194	NP		0						--	
S 5195	P		9	9					2.00	
S 5196	P		15	15					1.54	
S 5197	P		12	12					1.95	
S 5198	P		12	12					1.63	
S 5199	P		12	12					1.66	
S 5200	P		12	12					1.52	
S 5201	P		16	16					1.79	

* P = Pregnant; NP = Not Pregnant

** Not recorded

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 62

Appendix II

Date June 15, 1972Material Aspirin

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895Dose 250 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M**	F**			
A 5181	P		11	11					2.29	
A 5182	P		14	14					2.10	
A 5183	P		16	15				1	1.77	
A 5184	P		15	15					1.60	
A 5185	P		15	13				2	1.85	
A 5186	P		12	12						Aborted Day 13
A 5187	P		13	13					1.73	
A 5188	P		12	12					1.74	
A 5189	P		13	13					1.76	
A 5190	P		13	12				1	2.06	
A 5191	P		12	11				1	2.06	
A 5192	P		10	9				1	1.73	
A 5193	P		10	9				1	1.54	
A 5194	P		14	13	1				1.82	
A 5195	P		11	10				1	1.65	
A 5196	P		10	10					2.03	
A 5197	P		16	15				1	1.77	
A 5198	P		10	10					1.94	
A 5199	NP		0						--	
A 5200	P		13	13					1.94	
A 5201	P		10	8				2	1.59	

* P = Pregnant; NP = Not Pregnant

** Not recorded

FOOD & DRUG RESEARCH LABORATORIES, INC.

Group 67

Appendix II

Date June 15, 1972Material FDA 71-13

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895cDose 17 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex **		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
C 5001	P		9	7				2	2.11	
C 5002	P		12	12					2.11	
C 5003	P		13	13					2.01	
C 5004	P		8	5				3	2.07	
C 5005	P		11	11					1.86	
C 5006	P		17	17					2.14	
C 5007	P		10	10					1.99	
C 5008	P		13	12					1.98	
C 5009	P		14	14					1.93	
C 5010	P		11	10				1	1.89	
C 5011	P		15	15					2.01	
C 5012	P		13	11				2	1.57	
C 5013	P		16	16					1.82	
C 5014	P		12	12					2.00	
C 5015	P		8	8					2.08	
C 5016	P		15	15					1.80	
C 5017	P		13	13					1.71	
C 5018	P		10	10					2.05	
C 5019	P		13	13					1.83	
C 5020	P		15	12				3	2.03	

* P = Pregnant; NP = Not Pregnant

** Not recorded

FOOD AND DRUG RESEARCH LABORATORY, INC.

Group 68

Appendix II

Date June 15, 1972

Material FDA 71-13

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895c

Dose 80 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex**		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
C 5031	P		13	13					1.99	
C 5032	P		10	10					1.85	
C 5033	P		11	11					2.00	
C 5034	P		12	11				1	2.05	
C 5035	P		11	11					1.90	
C 5036	P		12	12					1.61	
C 5037	P		16	16					2.15	
C 5038	P		10	9				1	1.80	
C 5039	P		11	11					2.03	
C 5040	P		12	10	1			1	1.95	
C 5041	P		11	11					1.79	
C 5042	NP		0						--	
C 5043	P		12	12					1.90	
C 5044	P		15	13				2	2.03	
C 5045	P		14	14					1.88	
C 5046	P		11	11					1.71	
C 5047	P		13	13					1.92	
C 5048	P		11	10					1.43	
C 5049	P		13	11				2	1.67	
C 5050	NP		0						--	
C 5051	NP		0						--	
C 5052	P		17	15				2	1.99	
C 5053	P		12	12					1.76	

* P = Pregnant; NP = Not Pregnant

** Not recorded

FOOD & DRUG RESEARCH LABORATORIES, INC.

Group 69

Appendix II

Date June 15, 1972

Material FDA 71-13

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895c

Dose 370 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex **		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
C 5061	NP		0						--	
C 5062	P		8	6				2	2.38	
C 5063	P		12	12					2.19	
C 5064	P		10	7	1			2	1.85	
C 5065	P		11	10				1	2.22	
C 5066	P		10	10					2.07	
C 5067	P		14	14					2.02	
C 5068	P		13	12				1	1.89	
C 5069	P		14	12				2	2.01	
C 5070	P		15	14				1	1.73	
C 5071	P		16	16					1.95	
C 5072	NP		0						--	
C 5073	P		11	11					1.65	
C 5074	P		13	12				1	1.75	
C 5075	P		14	14					2.06	
C 5076	P		10	10					1.90	
C 5077	P		13	13					1.68	
C 5078	P		10	10					1.95	
C 5079	P		16	15				1	1.98	
C 5080	P		15	15					1.86	
C 5081	P		16	15				1	1.76	
C 5082	P		15	14				1	1.77	

* P = Pregnant; NP = Not Pregnant

** Not recorded

FOOD & DRUG RESEARCH LABORATORY, INC.

Group 70

Appendix II

Date June 15, 1972

Material FDA 71-13

Reproduction Data in Hamsters (Individual)

Laboratory No. 0895c

Dose 1700 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex**		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
C 5091	P		15	14				1	2.16	
C 5092	P		11	11					2.06	
C 5093	P		12	12					1.99	
C 5094	P		13	13					2.16	
C 5095	P		13	13					2.06	
C 5096	P		13	13					1.85	
C 5097	P		15	15					2.01	
C 5098	P		14	14					1.86	
C 5099	P		8	8					1.98	
C 5100	P		15	15					1.79	
C 5101	P		11	0				11	--	
C 5102	P		14	14					1.81	
C 5103	P		13	10	1			2	1.89	
C 5104	P		11	11					1.85	
C 5105	P		12	12					1.60	
C 5106	P		13	13					1.79	
C 5107	P		12	11				1	1.83	
C 5108	P		12	12					1.48	
C 5109	P		14	14					2.01	
C 5110	P		15	15					1.86	

* P = Pregnant; NP = Not Pregnant

** Not recorded

RABBITS

Food and Drug Research Laboratories
INCORPORATED



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**FINAL
REPORT**

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date August 1, 1972

Laboratory No. 0896 c
Contract No. FDA 71-260

Sample: Fine tan powdered material

Marking: FDA 71-13 (Gum ghatti)

Examination Requested: Teratologic evaluation of FDA 71-13 in rabbits


Procedure: (See Appendix I)

Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination of the data, it is tentatively concluded that:

"The administration of up to 33 mg/kg (body weight) of the test material as a suspension in anhydrous corn oil to pregnant rabbits for 13 consecutive days had no discernable effect on nidation or on maternal or fetal survival. The number and type of abnormalities seen in fetal soft or skeletal tissues derived from this group of does did not differ from the number occurring spontaneously in the sham-treated controls. However, in 2 groups of dams dosed at 150 and 700 mg/kg (body weight), significant maternal toxicity ensued with the loss of a majority of the animals. Death was preceded by severe bloody diarrhea and urinary incontinence with anorexia for 48 to 72 hours terminally. At autopsy, no gross pathological findings were seen other than marked hemorrhage in the mucosa of the small intestine. Does which survived this high dose and bore living young to term remained outwardly normal and the offspring were likewise normal in all respects. It is concluded that this test substance was not a teratogen in the rabbit.

FOOD AND DRUG RESEARCH LABORATORIES, INC.


Kenneth Morgareidge, Ph.D.
Vice President

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Comment: Attention is called to the fact that this is the seventh of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs: each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 61 & 62; 67 through 70

Material: FDA 71-13

Table 1

Fate Summary
(Rabbits)

Date June 15, 1972

Laboratory No. 0896 c

Group	Material	Dose ** mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
61	Sham	0	15	13	12	10
62	6-AN	2.5	15	10	14	9
67	FDA 71-13	7.0	15	12	15	12
68	FDA 71-13	33.0	15	14	11	11
69	FDA 71-13	150.0	15	14	10	10
70	FDA 71-13	700.0	15	12	5	2

* Positive Control: 6-amino nicotinamide dosed on Day 9

** Administered as suspension in anhydrous corn oil; 1.0 ml per kg of body weight

Group: 61 & 62; 67 through 70 FOOD & DRUG RESEARCH LABORATORY, INC.

Date June 15, 1972

Material: FDA 71-13

Table 2
Reproduction Data
(Rabbits)

Laboratory No. 0896 c

Group:	61	62	67	68	69	70
Dose (mg/kg):	Sham	6-AN**	7.0	33.0	150.0	700.0
Pregnancies						
Total No.	13	10	12	14	14	12
Abortions (before Day 29)	3	1	0	4	5	10
To term (on Day 29)	10	9	12	11	10	2
Corpora lutea						
Total No.	161	154	150	186	183	172
Average/dam	10.7	10.3	10.0	12.4	12.2	11.5
Live litters						
Total No.	10	8	12	10	8	2
Implant sites						
Total No. (at term)	47	49	60	60	42	15
Average/dam*	4.70	5.44	5.00	5.45	4.20	7.5
Resorptions						
Total No.	7	17	11	9	7	5
Dams with 1 or more sites resorbed	3	8	5	6	5	1
Dams with all sites resorbed	0	1	0	0	2	0
Per cent partial resorptions	30.0	88.9	41.7	50.0	50.0	50.0
Per cent complete resorptions	----	11.1	----	----	20.0	----
Live fetuses						
Total No. (at term)	40	31	49	51	35	10
Average/dam*	4.00	3.44	4.08	4.64	3.50	5.00
Dead fetuses						
Total No.	0	1	0	0	0	0
Dams with 1 or more dead	----	1	----	----	----	----
Dams with all dead	----	0	----	----	----	----
Per cent partial dead	----	11.1	----	----	----	----
per cent all dead	----	----	----	----	----	----
Average fetus weight, g	36.1	32.4	37.9	35.4	29.6	34.6

* Includes only those dams found bearing live fetuses at term.

** Positive control: 2.5 mg/kg 6-amino nicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 & 62; 67 through 70

Laboratory No. 0896 c

Table 3

Material FDA 71-13

Date June 15, 1972

Summary of Skeletal Findings *
(Rabbits)

Findings	Group No.	61	62	67	68	69	70
	Dose (mg/kg)	Sham	6-AN**	7.0	33	150	700
Live Fetuses Examined (at term)		40/10	29/8	49/12	78/9 ^a	35/8	10/2
Sternebrae							
Incomplete oss.		3/1	4/3	1/1	6/4	3/3	2/2
Scrambled			1/1				
Bipartite		3/3	5/5	1/1			
Fused		3/2	6/6	1/1		1/1	
Extra			1/1				
Missing							
Other							
Ribs							
Incomplete oss.							
Fused/split			2/2				
Wavy			3/1				
Less than 12							
More than 13							
Other							
Vertebrae							
Incomplete oss.							
Scrambled			9/5				
Fused							
Extra ctrs. oss.							
Scoliosis			7/4				
Tail defects			21/5		1/1		
Other							
Skull							
Incomplete closure							
Missing							
Craniostosis			1/1		3/1		
Other							
Extremities							
Incomplete oss.							
Missing							
Extra							
Miscellaneous							
Cyclops & possible rudimentary head					1/1		

* Numerator=Number of fetuses affected; Denominator=Number of litters affected
 ** Positive control ^{a)} One litter lost

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 & 62; 67 through 70

Date June 15, 1972

Material FDA 71-13

Laboratory No. 0896 c

Table 3-a
Summary of Soft Tissue Abnormalities
(Rabbit)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
62	6-AN*	2.5	Z 6092	8	Anopia
				4	Club feet
			Z 6094	4	Anopia
					Club feet
			Z 6097	3	Anopia, club feet, cleft palate, hair lip
			Z 6100	4	Anopia
					Club feet
			Z 6101	1	Anopia

*6-amino nicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 61 & 62; 67 through 70

Date June 15, 1972

Species Rabbits

Table 4

Laboratory No. 0896 c

Average Body Weights*

Group	Material	Dose Level mg/kg	-----Day-----				
			0	6	12	18	29**
			----- kg -----				
61	Sham	0.0	2.23	2.26	2.31	2.35	2.44 (10)
62	6-AN	2.5	2.40	2.42	2.37	2.45	2.51 (9)
67	FDA 71-13	7.0	2.34	2.37	2.36	2.41	2.46 (12)
68	FDA 71-13	33.0	2.26	2.36	2.30	2.34	2.55 (11)
69	FDA 71-13	150.0	2.19	2.23	2.20	2.22	2.25 (10)
70	FDA 71-13	700.0	2.28	2.28	2.25	2.30	2.27 (2)

* Of pregnant dams

** Number of surviving dams in parentheses (c.f. Table 1)

*** Positive control: 6-amino nicotinamide dosed on Day 9.

a) Average based on weights of 9 does only



Appendix I

Teratology Study in Rabbits

Virgin, adult, Dutch-belted female rabbits were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. On Day 0, each doe was given an injection of 0.4 ml of human chorionic gonadotropin (400 IU) via the marginal ear vein. Three hours later, each doe was inseminated artificially with 0.3 ml of diluted semen from a proven donor buck using approximately 20×10^6 motile sperm according to the procedure described by Vogin et al (Pharmacologist 11, 282 (1969)). Beginning on Day 6 and continuing daily through Day 18 the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 12, 18, and 29 of gestation. All animals were observed daily for appearance and behavior, with particular attention to food consumption and body weight in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 29 all does were subjected to Caesarean section under surgical anesthesia, and the numbers of corpora lutea, implantation sites, resorption sites and live and dead fetuses were recorded. Body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality. In addition all fetuses underwent a detailed gross examination for the presence of external congenital abnormalities. The live fetuses of



each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities (by dissection). All fetuses were then cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 61

Appendix II

Date June 15, 1972

Material Sham

Reproduction Data in Rabbits (Individual)

Laboratory No. 0896

Dose 0.0

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
S 6091	P	15	8	8		2	6		36.4	
S 6092	NP	7	0						----	
S 6093	P	6	1	1		--	--		----	Died Day 13
S 6094	P	20	6	6		2	4		37.1	
S 6095	P	9	3	1		0	1	2	36.8	
S 6096	P	9	4	4		1	3		38.5	
S 6097	P	13	5	3		1	2	2	34.7	
S 6098	NP	3	0						----	
S 6099	P	13	6	6		2	4		39.2	
S 6100	P	8	3	3		0	3		24.0	
S 6101	P	12	5	2		1	1	3	36.7	
S 6102	P	14	6	6		--	--		----	Died Day 14
S 6103	P	14	4	4		1	3		36.4	
S 6104	P	9	4	4		--	--		----	Died Day 13
S 6105	P	9	3	3		1	2		40.9	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Appendix II

Date June 15, 1972

Group 62

Material 6-AN

Reproduction Data in Rabbits (Individual)

Laboratory No. 0896

Dose 2.5 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
Z 6091	NP	4	0						----	
Z 6092	P	21	9	8		3	5	1	33.8	
Z 6093	P	14	5	5		--	--		----	Died Day 22
Z 6094	P	20	10	8	1	2	6	1	26.8	
Z 6095	P	8	2			--	--	2	----	
Z 6096	NP	7	0						----	
Z 6097	P	11	6	3		1	2	3	27.1	
Z 6098	NP	5	0						----	
Z 6099	NP	6	0						----	
Z 6100	P	13	8	4		1	3	4	33.8	
Z 6101	P	12	5	1		0	1	4	32.1	
Z 6102	P	8	3	2		1	1	1	36.4	
Z 6103	P	7	4	3		-	1-	1	37.8	
Z 6104	NP	8	0						----	
Z 6105	P	10	2	2		1	1		31.6	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES INC.

Group 67

Appendix II

Date June 15, 1972

Material FDA 71-13

Reproduction Data in Rabbits (Individual)

Laboratory No. 0896 c

Dose 7.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
C 6001	P	17	9	9		3	6		40.4	
C 6002	P	15	5	5		2	3		39.7	
C 6003	NP	5	0						----	
C 6004	NP	3	0						----	
C 6005	P	12	6	4		1	3	2	38.5	
C 6006	P	9	5	1		0	1	4	30.0	
C 6007	P	11	8	8		3	5		35.0	
C 6008	P	8	4	2		1	1	2	39.5	
C 6009	P	10	3	1		1	0	2	34.7	
C 6010	NP	3	0						----	
C 6011	P	15	6	5		2	3	1	43.5	
C 6012	P	6	1	1		0	1		43.1	
C 6013	P	12	5	5		3	2		34.9	
C 6014	P	7	2	2		1	1		37.2	
C 6015	P	17	6	6		3	3		38.5	

* P = Pregnant; NP = Not Pregnant

Appendix II

Date June 15, 1972

Group 68

Material FDA 71-13

Reproduction Data in Rabbits (Individual)

Laboratory No. 0896 c

Dose 33.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
C 6016	P	9	3			--	--	3	----	
C 6017	P	13	6	6		3	3		32.5	
C 6018	P	12	7	6		2	4	1	34.7	
C 6019	P	16	12	10		3	7	2	29.7	
C 6020	P	12	5	5		--	--		----	
C 6021	P	14	5	4		2	2	1	39.4	Aborted Day 18
C 6022	P	8	2					2	----	Died Day 16
C 6023	P	12	3					3	----	Died Day 26
C 6024	P	17	5	5		1	4		37.9	
C 6025	NP	0	0						----	Died Day 21
C 6026	P	13	4	4		2	2		39.8	
C 6027	P	10	2	2		1	1		37.4	
C 6028	P	23	6	6		2	4		31.3	
C 6029	P	13	5	4		1	3	1	43.7	
C 6030	P	14	5	4		2	2	1	27.2	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES INC.

Group 69

Appendix II

Date June 15, 1972

Material FDA 71-13

Reproduction Data in Rabbits (Individual)

Laboratory No. 0896 c

Dose 150.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
C 6031	P	13	6	6		3	3		35.0	
C 6032	P	12	7	7		3	4		38.0	
C 6033	P	12	7	7		2	5		32.5	
C 6034	P	5	1					1	----	
C 6035	P	17	9	9		--	--		----	Died Day 16
C 6036	P	8	3	2		1	1	1	41.5	
C 6037	P	21	7	7		3	4		18.8	
C 6038	P	8	3	2		2	0	1	40.4	
C 6039	P	19	14	14		--	--		----	Died Day 17
C 6040	P	21	12	12		--	--		----	Died Day 16
C 6041	P	15	11	11		--	--		----	Died Day 12
C 6042	P	8	3	3		1	2		38.2	
C 6043	P	9	3					3	----	
C 6044	P	7	2	1		0	1	1	2.96	
C 6045	NP	8	0						----	Died Day 20

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES INC.

Group 70

Appendix II

Date June 15, 1972

Material FDA 71-13

Reproduction Data in Rabbits (Individual)

Laboratory No. 0896 c

Dose 700.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Sex		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead	M	F			
C 6046	P	17	8	8		2	6		26.8	
C 6047	NP	12	0						----	
C 6048	P	5	1	1		--	--		----	Died Day 14
C 6049	P	12	5	5		--	--		----	Died Day 16
C 6050	P	9	2	2		--	--		----	Died Day 15
C 6051	P	12	7	2		0	2	5	42.4	
C 6052	NP	2	0						----	
C 6053	P	13	3	3		--	--		----	Died Day 13
C 6054	P	20	8	8		--	--		----	Died Day 16
C 6055	P	12	7	7		--	--		----	Died Day 16
C 6056	P	11	2	2		--	--		----	Died Day 18
C 6057	P	13	5	5		--	--		----	Died Day 10
C 6058	P	13	5	5		--	--		----	Died Day 10
C 6059	NP	6	0						----	
C 6060	P	15	6	6		--	--		----	Died Day 10

* P = Pregnant; NP = Not Pregnant